

Erectile Dysfunction Is Common among Patients with Gout

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ABSTRACT. Objective. To determine whether men with gout may have an increased prevalence of erectile dysfunction (ED) as compared with men without gout.

Methods. In this cross-sectional study, men aged 18–89 presenting to the rheumatology clinic between August 26, 2010, and May 13, 2013, were asked to participate. The presence of ED was determined by the Sexual Health Inventory in Men (SHIM). SHIM classifies ED into 1 of 5 categories: absent (22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe (1–7). Patient's history, physical examination, and recent laboratory studies were reviewed as well. Descriptive statistics and subgroup analyses were used to summarize the data.

Results. Of the 201 men surveyed, 83 had gout (control, $n = 118$). A significantly greater proportion of patients with gout (63, 76%) had ED versus patients without gout (60, 51%, $p = 0.0003$). A significantly greater proportion of patients with gout (22, 26%) had severe ED versus patients without gout (17, 15%, $p = 0.04$). Patients with gout had an average SHIM score of 14.4 versus 18.48 in patients without gout ($p < 0.0001$). There was a statistically significant association between gout and ED. The association remained significant after adjustment for age, hypertension, diabetes, and obesity.

Conclusion. ED is present in most men with gout and is frequently severe. We propose that patients with gout be routinely screened for ED. (J Rheumatol First Release May 1 2015; doi:10.3899/jrheum.141031)

Key Indexing Terms:
GOUT

ERECTILE DYSFUNCTION

Erectile dysfunction (ED) is common in the general population, affecting about 50% of 40- to 70-year-old men¹. The National Institutes of Health Consensus Development statement defined ED as the “inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse”². The likelihood of ED increases with age, but is not an inevitable consequence of aging².

The importance of cardiovascular (CV) disease (CVD) as an underlying cause of ED is well established^{3,4}. This is not surprising because CVD and ED share mutual risk factors such as diabetes mellitus (DM), hypertension (HTN),

advanced age, hypercholesterolemia, obesity, metabolic syndrome, certain medications such as antidepressants, and tobacco abuse^{1,3,5,6}.

New evidence shows that hyperuricemia and inflammation may be independent risk factors for ED in addition to the established ones. In a recent study by Solak, *et al*⁷, of 312 men who underwent an exercise stress test because of chest pain, each 1 mg/dl increase in serum urate (SU) was associated with a 31% increased risk of ED. Compared with patients in the first quartile of SU level, those in the fourth quartile had a 2.6 times increased risk of ED. However, in an adjusted analysis for traditional CV risk factors, the relationship with SU was no longer significant. Another recent study, by Salem, *et al*⁸, evaluated SU level and the distribution of potential ED risk factors in 251 men with newly diagnosed ED versus 252 age-matched controls without ED. A significant difference was found between mean SU levels in men with ED (6.12 mg/dl) versus men without ED (4.97 mg/dl). The men in the highest tertile of SU level had a 6-fold increased risk of ED compared with men in the lowest tertile. Each 1 mg/dl increase in SU level was associated with a 2-fold increased risk of ED.

Inflammation, too, plays an important role in ED^{9,10}. Low levels of interleukin 6 (IL-6) and fibrinogen exclude the presence of ED in patients with coronary artery disease (CAD) or with unfavorable risk factors⁹. It has been shown that plasma levels of high-sensitivity C-reactive protein

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(CRP) were significantly higher in patients with ED compared with patients without ED^{11,12}.

We did not find any publications on PubMed in the English medical literature investigating whether gout is associated with ED. We hypothesized that men with gout may have an increased prevalence of ED as compared with men without gout.

MATERIALS AND METHODS

Our study was a cross-sectional study of men aged 18–89 years presenting to the Rheumatology clinic with any form of arthritis between August 26, 2010, and May 13, 2013. The study protocol was approved by the University of Medicine and Dentistry of New Jersey's institutional review board, and all the participants signed informed consent forms before recruitment.

Included patients were asked to complete the Sexual Health Inventory in Men (SHIM) questionnaire. The SHIM sample was dependent on the availability of the authors. Patients attending clinic more frequently were more likely to be included. SHIM is an established, valid, and reliable questionnaire for determining the presence and severity of ED. SHIM has been shown to have high internal consistency (0.90), test-retest repeatability ($r = 0.84$), and construct (concurrent, convergent and discriminant) validity¹³. SHIM is a 5-item erectile function domain also known as the International Index of Erectile Function (IIEF) questionnaire¹³. SHIM consists of 5 questions. For each of the 5, the subject indicates an answer between 0 and 5. The prevalence of ED is generally based on a SHIM score of 21 or less. SHIM classifies ED into 1 of 5 categories: absent (22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe (1–7).

Gout diagnosis was reassessed retrospectively by investigating the medical reports. Authors doing chart review were not aware of the results of the SHIM. We accepted the diagnosis of gout if there was documentation of monosodium urate crystals aspirated from an affected joint or tophus and if not, clinical characteristics recorded were sufficient to fulfill the preliminary criteria for the classification of the acute arthritis of primary gout¹⁴.

The patients filled in a questionnaire regarding their disease, other comorbidities, and medications. In addition, the patient's full medical history with special attention to CVD risk factors and medications was reviewed. We assessed the effect of comorbidities such as heart disease, HTN, hypercholesterolemia, DM, smoking habits, and testosterone levels on sexual health assessed by SHIM. In addition, a thorough physical examination, as well as recent laboratory studies including SU, lipid profile, white blood cell count, glycosylated hemoglobin, CRP, and glomerular filtration rate (GFR) were reviewed.

The dependent variable used was SHIM. Baseline variables were calculated as mean \pm SD and median and interquartile range for continuous variables, and as frequencies and percentages for categorical variables. We compared the characteristics of men with gout versus men without gout and their responses to the SHIM questionnaire using the chi-square test and standard univariate statistics. Clinical characteristics of men in each category of ED (none, mild to moderate, and severe) were compared for trend using the Mantel-Haenszel chi-square test and ANOVA for trend on ranks for categorical and continuous variables, respectively. Pearson chi-square test and Mann-Whitney U tests were also reported for any ED (all categories) versus no ED.

We collected variables that were pertinent to the question of ED. We used a multivariable logistic regression analysis adjusting for whether a patient had gout; age; comorbidities such as depression, diabetes, HTN, elevated cholesterol, prostate disease, GFR, heart disease; and smoking status to identify factors associated with the odds of getting ED.

RESULTS

There were 201 men included in the study, all seen between August 26, 2010, and May 13, 2013. Two patients declined

to participate in the study. Eighty-three patients had gout and 118 served as the control group. Baseline demographic and clinical characteristics are shown in Table 1. Patients with gout versus those without gout were comparable in terms of total cholesterol and CRP levels as well as in the frequencies of age, depression, peripheral vascular disease, prostate disease, and alcoholism. However, patients with gout were heavier and had more HTN and heart disease, as well as higher SU and triglyceride levels, whereas there were more active smokers among patients without gout. Testosterone levels were checked in $\leq 5\%$ of patients. Sixty-seven patients with gout (80.7%) versus 76 patients without gout (64.4%) had ≥ 2 underlying comorbidities.

The most common diseases in patients without gout included rheumatoid arthritis (RA; $n = 27$), osteoarthritis ($n = 27$), psoriatic arthritis ($n = 16$), ankylosing spondylitis ($n = 10$), systemic sclerosis (SSc; $n = 9$), polymyalgia rheumatica ($n = 6$), low back pain ($n = 5$), systemic lupus erythematosus ($n = 4$), granulomatosis with polyangiitis ($n = 2$), and other ($n = 6$).

A significantly greater proportion of patients with gout (63, 76%) had ED versus patients without gout (60, 51%, $p = 0.0003$). A significantly greater proportion of patients with gout (22, 26%) had severe ED versus patients without gout (17, 15%, $p = 0.04$). Forty-one of patients with gout (49%) versus 43 of the control group (37%) had mild-moderate ED ($p = 0.09$).

The mean SHIM score of all patients was 16.81 with SD 7.93. Patients with gout had an average SHIM score of 14.4 and SD 8.11 versus 18.48 and SD 7.36 in patients without gout ($p < 0.0001$).

Univariate and multivariate analysis were conducted in associating ED with key risk factors such as gout, age, depression, diabetes, fasting glucose, HTN, elevated cholesterol level, prostate disease, GFR, and heart disease. The unadjusted and adjusted OR and their 95% CI of ED on these factors are listed in Table 2. The adjusted OR of ED on gout was 2.92 with 95% CI 1.41–6.06, suggesting that men with gout had almost 2-fold greater odds of getting ED than men without gout. With the bootstrap hypothesis testing method, we estimated the power of obtaining such a significant OR was 79%¹⁵.

ED was present in 23 patients with gout (96%) versus 19 patients without gout (79%, $p = 0.08$) whose age was ≥ 65 ($n = 48$). In patients with gout whose age was ≥ 65 , severe ED was present in 15 (60%) versus 8 patients without gout (32%, $p = 0.0002$), and mild-moderate ED was present in 10 patients with gout (40%) whose age was ≥ 65 versus 14 patients without gout (56%, $p = 0.26$).

Fifty patients with gout (60%) were receiving urate-lowering therapy (ULT) and/or colchicine. ULT included febuxostat (40 mg daily, $n = 13$ and 80 mg daily, $n = 3$), and daily doses of allopurinol 100 mg ($n = 12$), 200 mg ($n = 6$), 300 mg ($n = 8$), 400 mg ($n = 2$), and 500 mg ($n = 1$).

Table 1. Patient demographics and clinical characteristics. Values are mean \pm SD or n (%) unless otherwise specified.

Characteristics	Patients with Gout, n = 83	Patients without Gout, n = 118	p
Age, yrs	56.67 \pm 14.29	53.52 \pm 13.70	0.12
Height, inches	68.41 \pm 3.26	69.47 \pm 3.23	0.03
Weight, lbs	219.62 \pm 44.98	201.53 \pm 39.72	0
Past smoker	26 (31.3)	26 (22.03)	0.45
Current smoker	52 (63.4)	85 (72.03)	0.29
BMI, kg/m ²	33.07 \pm 6.05	29.54 \pm 5.25	0
Systolic BP, mmHg	127.93 \pm 17.18	126.03 \pm 14.32	0.4
Diastolic BP, mmHg	78.59 \pm 10.91	77.31 \pm 8.39	0.37
Total cholesterol	183.65 \pm 45.04	175.87 \pm 37.35	0.24
TG	204.31 \pm 146.66	121.28 \pm 71.29	0
HDL	43.71 \pm 9.76	48.74 \pm 15.04	0.01
LDL	104.74 \pm 35.15	102.17 \pm 39.26	0.68
Serum urate, mg/dl	7.42 \pm 2.20	6.05 \pm 1.37	0
Fasting glucose	111.34 \pm 36.24	99.35 \pm 20.87	0.01
HbA1c	6.28 \pm 1.23	5.87 \pm 0.52	0.14
WBC	7.06 \pm 2.26	9.17 \pm 13.93	0.12
CRP	2.51 \pm 3.39	2.89 \pm 4.73	0.57
GFR, ml/min	65.50 \pm 21.57	69.78 \pm 23.21	0.2
Comorbidities			
Diabetes mellitus	12 (14.5)	11 (9.32)	0.7
Hypertension	54 (65.1)	61 (51.69)	0.15
Heart disease	17 (20.5)	14 (11.86)	0.52
Blood vessel disease	2 (2.4)	5 (4.24)	0.7
Elevated cholesterol	43 (51.8)	36 (30.51)	0.06
Pelvic injuries	0 (0.0)	0 (0.00)	1
Low testosterone levels	6 (7.2)	7 (5.93)	0.92
Depression	8 (9.6)	10 (8.47)	0.93
Prostate disease	9 (10.8)	12 (10.17)	0.96
Prostatectomy	2 (2.4)	1 (0.85)	0.57
Tophi	23 (27.7)	2 (1.69)	0
CKD, GFR ml/min			0.52
No, > 60	48 (60)	75 (66)	
Mild-moderate, 30-59	28 (35)	35 (31)	
Severe, \leq 29	4 (5)	3 (3)	

p values are based on (1) Student t tests for binary variables when all cell counts are greater than 5, or Fisher's exact test otherwise; (2) chi-square tests for categorical variables with more than 3 levels when all cell counts are greater than 5, or Monte Carlo simulations otherwise; (3) Student t tests for continuous variables. BMI: body mass index; BP: blood pressure; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: glycosylated hemoglobin; WBC: white blood cell; CRP: C-reactive protein; GFR: glomerular filtration rate; CKD: chronic kidney disease.

Table 2. Unadjusted and adjusted odds of patients getting ED.

Effect	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Gout	3.04 (1.64-5.66)	2.92 (1.41-6.06)
Age	1.06 (1.04-1.09)	1.06 (1.02-1.09)
Depression	2.38 (0.75-7.50)	1.76 (0.48-6.46)
Diabetes	1.92 (0.72-5.12)	1.15 (0.28-4.77)
Hypertension	2.09 (1.18-3.73)	1.32 (0.66-2.66)
Elevated cholesterol	2.09 (1.18-3.73)	1.24 (0.59-2.60)
Smoking	2.42 (1.31-4.47)	0.76 (0.18-3.17)
Prostate disease	2.97 (0.96-9.18)	1.21 (0.34-4.34)
GFR	0.99 (0.98-1.00)	1.01 (0.99-1.02)
Heart disease	3.91 (1.43-10.68)	2.16 (0.67-6.94)

ED: erectile dysfunction; GFR: glomerular filtration rate.

Thirty patients were taking chronic colchicine prophylaxis; of those, 26 patients were treated with ULT and 4 were not.

Twenty-three patients with gout (27.7%) had visible tophi on physical examination. Twenty patients with tophaceous gout (87%) had ED versus 43 patients without tophi (71%, $p = 0.12$). Severe ED was reported in 6 patients with tophaceous gout (26%) versus 22 patients without tophi (37%, $p = 0.44$), and mild-moderate ED in 12 patients with tophaceous gout (52%) versus 22 patients without tophi (37%, $p = 0.22$).

Duration of gout diagnosis prior to entering the study was divided into 4 periods (< 5 yrs, 5 to < 10 yrs, 10 to < 20 yrs, and \geq 20 yrs). There were 33 patients with gout < 5 years: 21 (64%) with ED and 8 (38%) with severe ED. In the group

(18 patients) with gout 5 to < 10 years, 14 (78%) had ED and 8 (43%) had severe ED. There were 17 patients with gout 10 to < 20 years: 12 (71%) with ED and 3 (25%) with severe ED. Finally, there were 11 patients with gout \geq 20 years: 10 (91%) with ED and 5 (45%) with severe ED. Chi-square tests showed that the proportions of ED and severe ED were not significantly different among the 4 periods.

DISCUSSION

We found ED to be present in most men with gout (76%), and the ED was frequently severe. We found the odds of getting ED in patients with gout to be almost 2 times greater than for men without gout. ED was significantly more common in patients with gout with disease duration greater than 20 years and patients with tophaceous gout. However, ED was common in all patients with gout, not just those with the highest gout burden. There was a statistically significant association between gout and ED, even after adjustment for age, HTN, obesity, and diabetes. The significance of our findings is further highlighted by the control group being composed of many patients with rheumatic diseases that have an increased prevalence of ED, such as RA¹⁶ and SSc^{17,18}. We found ED to be common in our patients, those with gout and the control group, and a major health problem. Previous studies have shown RA and patients with SSc to have an increased prevalence of ED^{16,17,18}.

We used the SHIM, a widely used scale for screening and diagnosis of ED and severity of ED in clinical practice and research, to diagnose ED in our patients. Studies have used the SHIM to diagnose ED in order to include patients with ED in studies¹⁹ and to estimate the prevalence of ED in patients with chronic diseases, as we did. The estimated prevalence of ED was 68% for men with diabetes²⁰, 70% for men with chronic stable CAD²¹, 81% for men with SSc, and 48% for men with RA¹⁸. Researchers and patients found the SHIM to be useful, quick, and inexpensive.

Our findings are important because ED, a common finding in patients with gout, is an independent predictor of future CV events. Endothelial dysfunction has an important role in the pathophysiology of ED. The small diameter of the cavernosal arteries and the relatively high content of endothelium-per-unit volume make the penile vascular bed a sensitive marker for CVD²². Because the penile arteries are small (1–2 mm) compared with the coronary arteries (3–4 mm), the same level of endothelial dysfunction and atherosclerosis may lead to a more significant reduction of blood flow in the penile arteries compared with those of the coronary arteries²³.

Studies have examined the ability of ED to predict the risk of future CV events (myocardial infarction, stroke, revascularization) and mortality. In a metaanalysis of 14 prospective cohort studies involving 92,757 men followed for a mean period of 6 years, ED increased significantly and independently of traditional risk factors of CV events, mortality,

myocardial infarction, cerebrovascular events, and all-cause mortality by 44%, 19%, 62%, 39%, and 25%, respectively²⁴. In men with known CVD, ED increased the risk of all-cause mortality by 90%²⁴. Of importance, the predictive ability of ED is higher in younger patients with ED²⁴.

It is, therefore, not surprising that patients with ED were found to have an increased rate of concomitant silent CAD¹⁰. In an angiographic study, about 1 in 5 men presenting with ED had angiographically documented silent CAD²⁵. These findings underscore the need to identify patients with ED needing further investigation for silent CAD²⁶.

ED symptoms appear to precede coronary events by 2 to 3 years^{9,27}.

The patient with ED, irrespective of whether he has established CVD, is “reclassified” into a higher risk category for future CV events²⁷. More aggressive treatment is warranted of CVD risk factors, commonly seen in our patients with gout, as well as a close followup. The diagnosis of ED should prompt an initial CV assessment based on the history and clinical examination to define the baseline risk according to the likelihood of silent or to the stage of clinically evident CAD²⁷.

Hyperuricemia and inflammation may be independent risk factors for ED in addition to the established ones. Uric acid can induce endothelial dysfunction, oxidative stress, inflammation, and microvascular disease, and this could provide a link between uric acid and CVD and ED, as well as other CAD risk factors²⁸. Could hyperuricemia explain part of the association between ED and gout? Would treatment of hyperuricemia improve erectile function? Studies should be performed to determine the potential benefit of lowering SU in patients with gout with ED in the presence or absence of CAD. In addition, inflammation plays an important role in ED^{11,12,28} and may be an important factor contributing to ED in patients with gout. Sexual performance assessed by the Erectile Function 5 (IIEF-5) score correlated inversely with circulating levels of the endothelial prothrombotic and inflammatory cytokines IL-1 β and IL-6^{9,10}. Correction of gouty inflammation may lead to improvement in erectile function.

Previously, the Campaign Against Cancer and Heart Disease study, using a community-based questionnaire of 2605 men, 256 (9.8%) conveying a history of gout, reported in abstract form²⁹ that ED, based on a polar (yes-no) question, was significantly more common among participants with gout as compared with participants without gout (39.8% vs 28.8%, $p < 0.001$). Men with gout were significantly more likely to have ED than men without gout, even after adjustment for age. However, the association was not observed after adjustment for obesity, HTN, and DM. The study was hampered by several limitations. Many participants were young and at a low CVD risk, and assessment of ED was based on a polar (yes-no) question and not on a validated questionnaire such as SHIM.

Our study has several strengths. Most importantly, these

data were derived from a large clinic-based cohort and include all patient ages. We used a validated outcome measure, SHIM, to evaluate ED. There are, however, several limitations. Cases of ED were ascertained through self-reported questionnaires. In addition, the SHIM does not assess sexual desire or orgasm and does not diagnose the etiology of the ED, only its presence and level of severity. Although every attempt was made to include all male patients coming to the Rheumatology clinic, inclusion was dependent on availability of NS and DR to enroll patients during clinic time.

ED is present in most men with gout and is frequently severe. Despite the importance of sexuality on the quality of life, little attention has been paid to the effect of gout on sexual function. A man with ED, even without cardiac symptoms, is a cardiac patient until proven otherwise. A diagnosis of ED should prompt an initial CV assessment based on the history and clinical examination to define the baseline risk according to the likelihood of silent or to the stage of clinically evident CAD. Increasing awareness of ED in patients with gout may lead to earlier medical attention, treatment, and evaluation of possible silent CVD. Patients do not volunteer sexual complaints; therefore, we propose that all men with gout be routinely screened for ED.

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